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(54) Title: A PROCESS FOR THE REDUCTION OF OXIRANYL EPOTHILONES TO OLEFINIC EPOTHILONES

(57) Abstract

The present invention relates to a process for the reduction of oxiranyl epothilones to olefinic epothilones.

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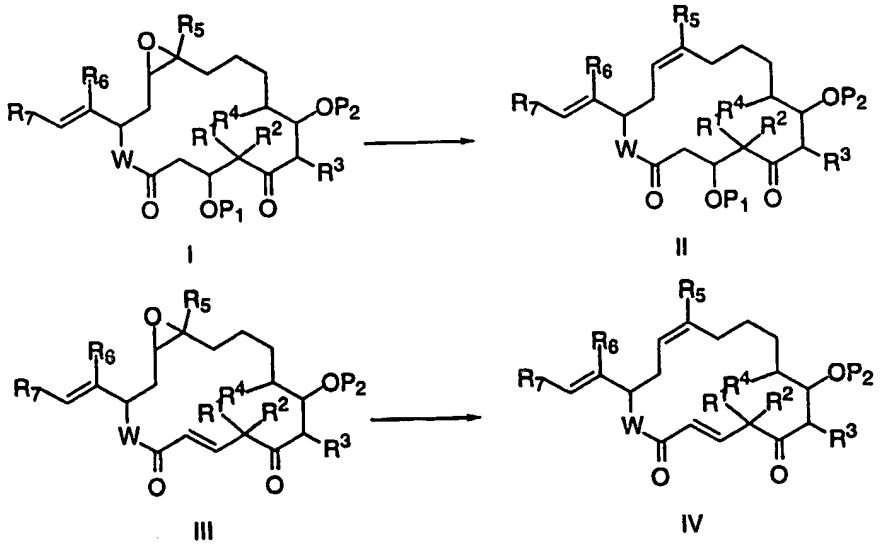
A PROCESS FOR THE REDUCTION OF OXIRANYL EPOTHILONES TO OLEFINIC EPOTHILONES

Brief Description of the Invention

The present invention is directed to a process for preparing compounds of formulas II and IV.



I II

III IV

The compounds of formulas I - IV are useful in the treatment of a variety of cancers and other abnormal proliferative diseases. Compounds of formula I are disclosed in Hofle et al., Angew. Chem. Int. Ed. Engl., 1996, 35, No 13/14; WO93/10121 published May 27, 1993 and WO97/19086 published May 29, 1997 and also Nicolaou et al., Angew Chem. Int. Ed. Engl., 1997, 36, 2097 and Danishefsky et al., Angew Chem. Int. Ed. Engl., 1997, 36, 2093. As used in the formulas I and II, and throughout the specification, the symbols have the following meanings:

W is O, NR_8;

R_1, R_2, R_3, R_4, R_5, R_6, are selected from the group H, alkyl, substituted alkyl, or aryl and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl;

R_7 is selected from the group consisting of H, alkyl, substituted alkyl, aryl, cycloalkyl, or heterocyclo;

R_8 is H, alkyl, or substituted alkyl, OH, O-alkyl, O-substituted alkyl;

P_1 and P_2 are selected from the group, H, alkyl, substituted alkyl, alkanoyl, substituted alkanoyl, aroyl, substituted aroyl, trialkylsilyl, aryl dialkylsilyl, diaryl alkylsilyl, triarylsilyl.

Detailed Description of the Invention

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkyoxy, heterocylooxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino,

thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido (e.g. SO_2NH_2), substituted sulfonamido, nitro, cyano, carboxy, carbamyl (e.g. $CONH_2$), substituted carbamyl (e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl; substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, cycloalkyloxy, heterocyclooxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, cycloalkylamino, heterocycloamino, dialkylamino, alkanoylamino, thiol, alkylthio, cycloalkylthio, heterocyclothio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by halo, hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

The term "cycloalkyl" refers to a optionally substituted, saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C3-C7 carbocyclic ring. Exemplary groups include cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary substituents include one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-

quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents include one or more alkyl groups as described above or one or more groups described above as alkyl substituents. Also included are smaller heterocyclos, such as, epoxides and aziridines.

The term "alkanoyl" refers to -C(O)-alkyl.

The term "substituted alkanoyl" refers to -C(O)-substituted alkyl.

The term "aroyl" refers to -C(O)-aryl.

The term "substituted aroyl" refers to -C(O)-substituted aryl.

The term "trialkylsilyl" refers to $-Si(alkyl)_3$.

The term "aryl dialkylsilyl" refers to $-Si(alkyl)_2(aryl)$.

The term "diaryl alkylsilyl" refers to $-Si(aryl)_2(alkyl)$.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

Use and Utility

The compounds of formula I - IV are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers, including (but not limited to) the following;

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;

- tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma;
- other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma;
- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscaroma, and osteosarcoma; and
- other tumors, including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

Compounds of formulas I - IV may also inhibit tumor angiogenesis, thereby affecting the growth of tumors. Such anti-angiogenesis properties of the compounds of formulas I and IV may also be useful in the treatment of certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

Compounds of formulas I - IV may induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of I - IV, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer (particularly, but not limited to follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostrate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including but not limited to systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal

muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

The compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formulas I - IV can be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate. Especially useful are cytotoxic drug combinations wherein the second drug chosen acts in a different phase of the cell cycle, e.g. S phase, than the present compounds of formulas I - IV which exert their effects at the G_2-M phase.

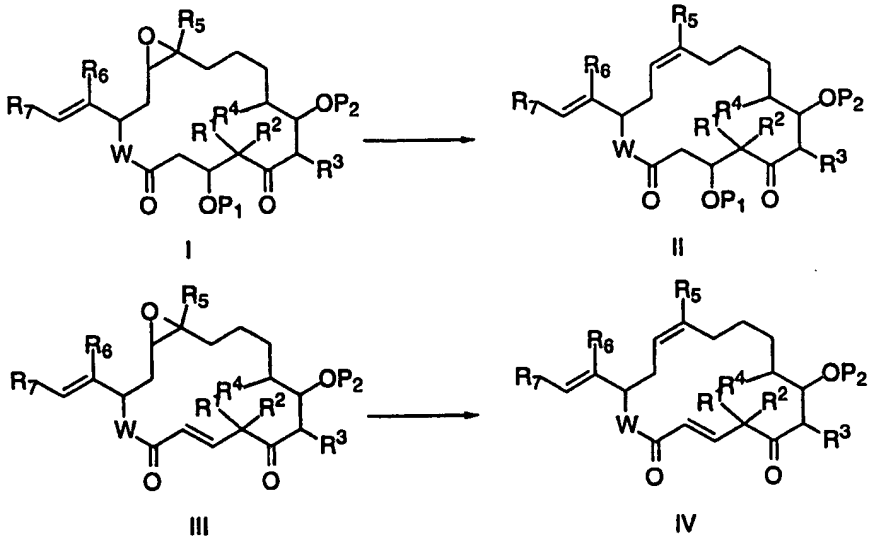
The present compounds may exist as multiple optical geometric and stereoisomers. Included within the present invention are all such isomers and mixtures thereof in the racemic form.

The compounds of this invention can be formulated with a pharmaceutical vehicle or diluent for oral, intravenous or subcutaneous administration. The pharmaceutical composition can be formulated in a classical manner using solid or liquid vehicles, diluents and additives appropriate to the desired mode of administration. Orally, the compounds can be administered in the form of tablets, capsules, granules, powders and the like. The compounds are administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Method of Preparation

Compounds of formulas II and IV are prepared from compounds of formulas I and III, as shown in Scheme 1. A compound of formula I or III afford compounds of formula II or IV when treated with a reactive metallocene such as titanocene, zirconocene or niobocene (see for example R. Schobert and U. Hohlein, Synlett (1990), 465-466.). Optionally, compounds of formulas II or IV where P_1 and/or P_2 are hydroxyl protecting groups such as silanes, e.g., trialkylsilyl, and the like, can be deprotected by methods known in the art to provide compounds of formula II or IV where where P_1 and P_2 are hydrogen.

Scheme 1



Alternatively, other metal or metal-assisted reagents can be used for the conversion of a compound of formula I or III to a compound of formula II or IV, as listed below:

1) $N_2C(CO_2Me)_2$, cat $Rh_2(OAc)_4$
Martin, M.G.; Ganem, B. *Tett. Lett.* **1984**, *25*, 251.

2) $N_2C(CO_2Me)_2$, cat $[(n\text{-}C_7H_{15}CO_2)_2Rh]_2$
Rancher, S.; Ki-Whan, C.; Ki-Jun, H.; Burks, J. *J. Org. Chem.* **1986**, *51*, 5503.

3) Zn-Cu, EtOH
Kupchen, S.M.; Maruyama, M. *J. Org. Chem.* **1971**, *36*, 1187.

4) Mg(Hg), $MgBr_2$
Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G. *Chem. Commun.* **1970**, 144.

5) Cr
Gladysz, J.A.; Fulcher, J.G.; Togashi, S. *J. Org. Chem.* **1976**, *41*, 3647.

6) $FeCl_3$, *n*-BuLi
Fujisawa, T.; Sugimoto, K.; Ohta, H. *Chem. Lett.* **1974**, 883.

7) $TiCl_3$, $LiAlH_4$
McMurry, J.E.; Fleming, M.P. *J. Org. Chem.*. **1975**, *40*, 2555.
McMurry, J.E.; Silvestri, M.G.; Fleming, M.P.; Hoz, T.; Grayston, M.W. *J. Org. Chem.* **1978**, *43*, 3249.

8) $TiCl_4$, Zn
McMurry, J.E.; Silvestri, M.G.; Fleming, M.P.; Hoz, T.; Grayston, M.W. *J. Org. Chem.* **1978**, *43*, 3249.

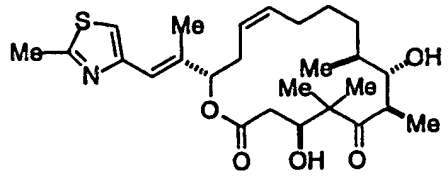
9) WCl_6, $LiAlH_4$
Fugiwara, Y.; Ishikawa, R.; Akiyama, F.; Teranishi, S. *J. Org. Chem.* **1978**, *43*, 2477.

10) $NbCl_5$, $NaAlH_4$
Sato, M.; Oshima, K. *Chem. Lett.* **1982**, 157.

11) VCl_3, Zn
Inokuchi, T.; Kawafuchi, H.; Torii, S. *Synlett* **1992**, *6*, 510.

12) WCl_6, *n*-BuLi
Sharpless, K.B.; Umbret, M.A.; Nieh, M.T.; Flood, T.C. *J. Am. Chem. Soc.* **1972**, *94*, 6538.

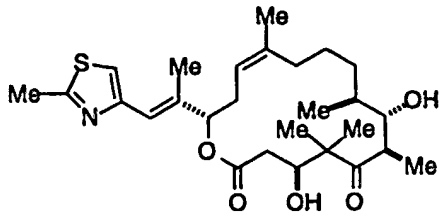
Example 1



[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Epothilone C]

To a two-necked flask was added chopped pieces of magnesium turnings (24 mg, 1.0 mmol). The flask was flame-dried under vacuum and cooled under argon. Bis(cyclopentadienyl)titanium dichloride (250 mg, 1.0 mmol) was added followed by anhydrous THF (5 mL). The stirring suspension was evacuated with low vacuum, and the reaction flask was refilled with argon. The red suspension became dark, turning a homogeneous deep green after 1.5h with nearly all the magnesium metal being consumed. An aliquot (3.5 mL, 0.70 mmol, 3.5 eq) was removed and cooled to -78 °C under argon. To this solution was added epothilone A (99 mg, 0.20 mmol, 1.0 eq). The reaction mixture was warmed to room temperature and stirred for 15 min. The volatiles were removed *in vacuo* and the residue was chromatographed two times on silica (25g), eluting with 35% EtOAc/hexanes to give 76 mg (80%) of the title compound as a pale yellow viscous oil.

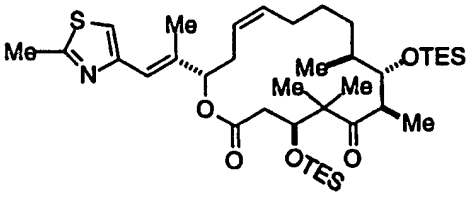
Example 2



[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Epothilone D]

To anhydrous THF (5 ml) at -78 °C under argon was added WCl_6 (198 mg, 0.5 mmol) followed by *n*BuLi (0.625 ml of 1.6 *M* solution in hexanes, 1.0 mmol). The reaction was allowed to warm to room temperature over a 20 min period. An aliquot (0.50 ml, 0.05 mmol) of the tungsten reagent was removed and added to epothilone B (9.0 mg, 0.018 mmol) under argon and the reaction mixture was stirred for 15 min, and then quenched by the addition of saturated $NaHCO_3$ (1 ml). The reaction mixture was extracted with EtOAc (3 x 1 ml), the combined extracts dried (Na_2SO_4), filtered, and the volatiles were removed under vacuum. The residue was chromatographed with 35% EtOAc/hexanes to give the title compound (7.0 mg, 0.014 mmol). MS *m/z*: 492.3 (M^++H).

Example 3



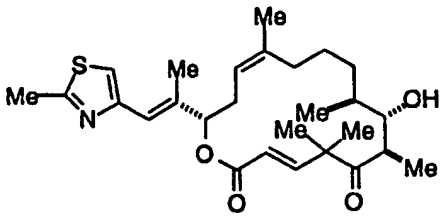
[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Triethylsilyloxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Bis-Triethylsilyl Epothilone C]

Et_3SiCl (4.15 mmol, 0.700 ml) was added to epothilone A (0.415 mmol, 205 mg), imidazole (2.07 mmol, 140 mg) and *i*-Pr_2EtN (6.22 mmol, 1.08 ml) in DMF (5 ml). The resulting solution was heated at 40 °C.

After 16 hrs, additional Et_3SiCl (2.07 mmol, 0.350 ml) and *i*-Pr_2EtN (4.15 mmol, 0.725 ml) were added and the resulting solution stirred at 60 °C for 48 hrs. The reaction was concentrated, and the residue was purified with flash chromatography (10% EtoAc/Hexanes). Bis-triethylsilyl epothilone A was isolated as colorless oil (264 mg, 88%). MS (M^++H) 722.

To anhydrous THF (5 ml) at -78 °C under argon was added WCl_6 (198 mg, 0.5 mmol) followed by nBuLi (0.625 ml of 1.6 *M* solution in hexanes, 1.0 mmol). The reaction was allowed to warm to room temperature over a 20 min period. An aliquot (1.0 ml, 0.089 mmol) of the tungsten reagent was removed and added to bis-triethylsilyl epothilone A (22.5 mg, 0.031 mmol) under argon and the reaction stirred for 20 min then quenched by the addition of saturated $NaHCO_3$ (1 ml). The reaction mixture was extracted with EtOAc (3 x 1 ml), the combined extracts dried (Na_2SO_4), filtered, and the volatiles were removed under vacuum. The residue was chromatographed with 10% EtOAc/hexanes to give the title compound (13.6 mg, 0.019 mmol) in 62% yield. MS *m/z*: 706.5 (M^++H).

Example 4



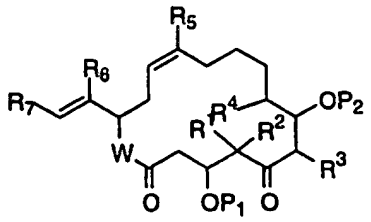
[7R-[7R*,8S*,9S*,15R*(E)]]-8-Hydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-3(E),13(Z)-cyclohexadecadiene-2,6-dione.

The title compound was prepared following the procedure described in Example 2. From 10 mg of [1S-[1R*,3R*(E),10S*,11S*,12R*,16S*]]-11-hydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadec-6-ene-5,9-dione (prepared from epothilone B using the procedure described in

PCT/EP96/05080 for the analogous conversion of epothilone A), 4.5 mg of title compound was obtained. MS 474 $(M+H)^+$.

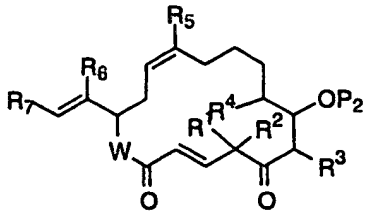
What is claimed:

1. A process to produce a compound of the formulas



II

or



IV

wherein

W is O, NR_8;

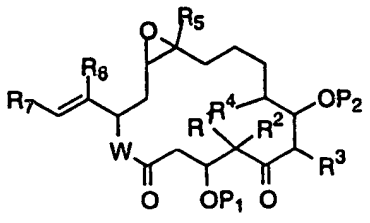
R_1, R_2, R_3, R_4, R_5, R_6, are selected from the group H, alkyl, substituted alkyl, or aryl and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl;

R_7 is selected from the group consisting of H, alkyl, substituted alkyl, aryl, cycloalkyl, or heterocyclo;

R_8 is H, alkyl, or substituted alkyl, OH, O-alkyl, O-substituted alkyl; and

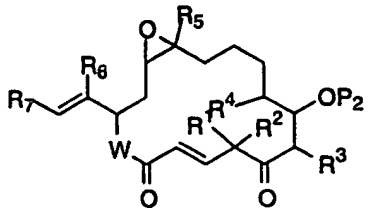
P_1 and P_2 are selected from the group, H, alkyl, substituted alkyl, alkanoyl, substituted alkanoyl, aroyl, substituted aroyl, trialkylsilyl, aryl dialkylsilyl, diaryl alkylsilyl, triarylsilyl.

Which comprises reacting a compound of the formula



I

or



III

wherein W, R_1, R_2, R_3, R_4, R_5, R_7, R_8, P_1 and P_2, are as above with a metal or metal assisted reagent selected from the group consisting of a reactive metallocene; [$N_2C(CO_2Me)_2$, cat Rh_2,$(OAC)_4$]; [$N_2C(CO_2Me)_2$, cat$(n\text{-}C_7H_{15}CO_2)_2$ Rh]$_2$; [Zn-Cu, EtOH]; [Mg(Hg), MgBr]; Cr; [$FeCl_3$, n-BuLi]; [$TiCl_3$, $LiAlH_4$]; [$TiCl_4$, Zn]; [WCl_6, $LiAlH_4$,] [$NbCl_5$, $NaAlH_4$]; [VCl_3,Zn] and [WCl_6, n-BuLi].

2. The process of claim 1 wherein the metal or metal assisted reagent is a metallocene.

3. The process of claim 2 wherein the metallocene is selected from the group consisting of titanocene, zirconocene or niobocene.

4. The process of claim 1 wherein the metal or metal assisted reagent is [WCl_6, n-BuLi].

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25464

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 493/04, 417/06, 277/24, 493/08; A61K 31/425;
US CL :540/451; 549/265, 266, 271
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/265, 266, 271

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/19086 A1 (HOFLE et al.) 05 June 1993, pages 1-4.	1-4
Y	SCHOBERT et al. Reduction and Isomerization of Oxiranes and alpha-Diazoketones by Various Early Transition Metallocenes. Synlett. August 1990, No. 8, pages 465-466, see entire document.	1-4
Y	SHARPLESS et al. Lower Valent Tungsten Halides. A New Class Of Reagents For Deoxygenation Of Organic Molecules. Journal of the American Chemical Society. 06 September 1972, Vol. 94, No.18, pages 6538-6540, see entire document.	1-4
A	WO 93/10121 A1 (HOFLE et al.) 27 May 1993.	1-4

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
12 JANUARY 1999

Date of mailing of the international search report
02 FEB 1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25464

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NICOLAOU et al. Designed Epothilones: Combinatorial Synthesis, Tubulin Assembly Properties, and Cytotoxic Action Against Taxol-Resistant Tumor Cells. Angew. Chem. Int. Ed. Engl. 1997, Vol. 36, No. 19, pages 2097-2102.	1-4
A	SU et al. Structure - Activity Relationships of The Epothilones and the First In Vivo Comparison With Paclitaxel. Angew. Chem. Int. Ed. Engl. 1997, Vol. 36, No. 19, pages 2093-2096.	1-4